JSLS

The Use of Transvaginal Sonography and Vaginoscopic Hysteroscopy in Women on Tamoxifen

Minas Paschopoulos MD, Emmanuel Kontostolis MD, Evangelos D. Lolis MD, George Koliopoulos MD, Yannis Alamanos MD, Evangelos Paraskevaidis MD

ABSTRACT

Background and Objectives: Long-term administration of tamoxifen causes endometrial changes. The aim of this study was to evaluate the role of transvaginal sonography and vaginoscopic hysteroscopy in the screening of patients on tamoxifen.

Methods: Seventy patients with breast cancer treated with tamoxifen 20 mg daily underwent transvaginal sonography and vaginoscopic hysteroscopy, a modified relatively painless approach, at the beginning of the treatment and at a follow-up visit approximately 9 months after its initiation.

Results: At the follow-up visit, the mean uterine dimensions and mean endometrial thickness as measured by ultrasound were significantly larger, and pulsatility and resistance indices of the uterine arteries as measured by Doppler were significantly lower. Sonography revealed abnormal endometrial thickness in 73% (51 of 70) of the patients, and 83% (58 of 70) had hysteroscopical changes. Sonography missed 1 case of endometrial adenocarcinoma.

Conclusions: Vaginoscopic hysteroscopy, an approach that causes reduced pain, can add significantly to the sensitivity of transvaginal sonography for the detection of endometrial changes in patients with breast cancer receiving tamoxifen. It is recommended for every patient prior to the initiation of treatment and at the follow-up visits.

Key Words: Tamoxifen, Vaginoscopic hysteroscopy, Transvaginal sonography, Endometrium.

Department of Obstetrics & Gynecology, Ioannina University Hospital, Ioannina, Greece (all authors).

Address reprint request to: Minas Paschopoulos MD, Opl. Poutetsi 2, 45332 Ioannina, Greece. Fax: 01130-651-99788, E-mail: paschomi@acropolis.net

INTRODUCTION

Tamoxifen is a nonsteroid antiestrogen, which has been principally used successfully in the adjuvant treatment and chemoprevention of disseminated receptor-positive breast cancer, particularly in postmenopausal women. It has been established that the long-term administration of tamoxifen causes several changes in the endocervix and endometrium (atrophy, polyposis, proliferation, vascular changes),[1] and indications exist that women on tamoxifen may be at increased risk of developing endometrial carcinoma.[2] It is, therefore, reasonable that such women, even if they are asymptomatic, must be under careful surveillance.

Transvaginal ultrasonography, sonohysterography, and hysteroscopy have been used in the examination of such women. However, controversy exists regarding the most optimal method of screening, but in most of the comparative studies the method that was used was conventional hysteroscopy. In this study, we used vaginoscopic hysteroscopy,[3] a relatively new and painless approach, transvaginal ultrasonography, and cytopathology for the investigation of tamoxifen-induced endometrial changes, and compared their performance.

MATERIALS AND METHODS

The study population consisted of 70 patients (mean age: 57.6 years ± 7.1 SD, range: 42 to 71) who had undergone modified radical mastectomy for breast cancer in our department and were receiving 20 mg of tamoxifen daily orally.

Every woman underwent transvaginal sonography (TVS) and vaginoscopic hysteroscopy before the initiation of tamoxifen treatment. TVS was used for the measurement of uterine dimensions and endometrial thickness, and Doppler analysis was used for the calculation of pulsatility and resistance indices (PI and RI, respectively) of both uterine arteries. Endometrial thickness over 4 mm for postmenopausal and over 6 mm for premenopausal women was considered abnormal. We used a 5-MHz Toshiba transducer. Vaginoscopic hysteroscopy was performed using the rigid Hamou contact Microhysteroscope I of 5-mm diameter or the Bettocchi 3.5-mm hys-

teroscope (Karl Storz, Tuttligen, Germany), at 1 x magnification for panoramic examination and at 20 x for microhysteroscopy. The vagina and the uterus were dilated with carbon dioxide. The procedure has been previously described in detail.[4] Vaginoscopic hysteroscopy was well tolerated by approximately 96% (67 of 70) of our patients, and no anesthesia (general or local) was used. Every woman was reevaluated with TVS and vaginoscopic hysteroscopy after a mean interval of 8.7 months (range: 5.2 to 13.4 months). At reevaluation, 62 women (88.6%) were asymptomatic, and 8 (11.4%) presented with abnormal uterine bleeding.

When hysteroscopy was suggestive of stromal proliferation, hysteroscopically directed biopsies were taken. When endometrial hypervascularity was found on hysteroscopy, the woman was followed up without biopsies. Endometrial polyps were resected if possible. In selected cases, where a high suspicion existed of malignancy based on the sonographic and hysteroscopic findings, dilatation and curettage (D&C) or endometrial resection and pathological examination were performed.

RESULTS

In most of the patients (64 of 70, 94%), the endometrial thickness in the initial sonographic examination was within normal limits. Six patients (6%) had endometrial thickening, and underwent D&C. The histopathological examination revealed focal or complex hyperplasia without atypia. The initial hysteroscopic findings were in accordance with the sonographic ones.

The follow-up sonographic examination, approximately 9 months after the initiation of tamoxifen administration, revealed abnormal endometrial thickness in 51 women (73%).

In the entire study population (70 women), the follow-up TVS measurements were significantly different from the initial ones **(Table 1)**. Specifically, the long axis of the uterus had a mean length of 52 mm as opposed to the previous TVS in which it was 42 mm. The mean maximum transverse diameter was 41 mm, but in the previous TVS it was 33 mm ($P < 0.001$). The endometrial thickness reached 7.9 ± 3.6 mm compared with 4.5 ± 1.8 mm in the initial TVS examination ($P < 0.001$). The mean PI and RI of the uterine arteries were 2.1 ± 0.5 and 0.83 ± 0.07, respectively, and they were significantly lower than those calculated before the initiation of tamoxifen administration 2.7 ± 0.16 and 0.88 ± 0.02, respectively ($P < 0.001$).

The hysteroscopic examination performed after the TVS revealed changes in 58 (83%) women. Specifically, we noted:

1. Smooth, white epithelium of the vagina, endocervix, and endometrium (stromal proliferation) in 24 women [34.3%, 23 to 45.6% (95% CI)];
2. Presence of endocervical or endometrial polyp-like protuberances surrounded by hypervascularized endometrium in 13 women [18.6%, 9.3 to 27.9% (95% CI)];
3. Atypical endometrial hypervascularity as a simple finding in 19 women [27.1%, 16.5 to 37.7% (95% CI)];
4. Hysteroscopic image resembling adenocarcinoma of the endometrium, which was confirmed pathologically after a D&C in 2 women [2.8%, 0.1 to 6.7% (95% CI)].

Histopathological examination was in agreement with hysteroscopical findings in the 24 women where hysteroscopy was suggestive of stromal proliferation and in both cases where hysteroscopy was suggestive of adenocarcinoma. TVS missed 1 of 2 cases of histopathologically confirmed adenocarcinoma. In 9 of the 13 women with a hysteroscopical finding of endometrial polyp, the polyps could be resected and histopathological examination revealed tamoxifen polyps.

DISCUSSION

Although classically described as an estrogen antagonist, tamoxifen can activate certain estrogenic effects, and no

Table 1.
Ultrasonographic measurements (mean ± standard deviation) in the pretreatment and in the follow-up examination.

Measurements	Pretreatment	Follow-up	*P* value*
Long axis of the uterus	42 ± 5 mm	52 ± 7 mm	<.001
Maximum transverse diameter	33 ± 4 mm	41 ± 5 mm	<.001
Endometrial thickness	4.5 ± 1.8 mm	7.9 ± 3.6 mm	<.001
Pulsatility index	2.7 ± 0.16	2.1 ± 0.5	<.001
Resistance index	0.88 ± 0.02	0.83 ± 0.07	<.001

* *P* value estimated with the Student's *t*-test.

doubt in some circumstances this drug can act as an estrogen agonist causing stromal proliferation, endocervical, or endometrial polyp-like protuberances and endometrial hypervascularity.[1] This is also confirmed by our study.

It has been established that women on tamoxifen should be evaluated for endometrial changes. The value of TVS in the follow-up of such women has been well-documented,[5] and in 1 study it was even found to be superior to office hysteroscopy.[6] However, evidence suggests that TVS has a high number of false-positive findings.[7] In this study, we noted abnormal sonographic findings in 73% of the patients on tamoxifen and abnormal hysteroscopic findings in 83%. With TVS, those lesions appeared as an abnormal endometrial thickness, but with vaginoscopic hysteroscopy they were more specified (polyps, protuberances, hypervascularity, and other such things). One of the main points against hysteroscopy as a screening test in women receiving tamoxifen is its limited acceptability from the patient. Considering that vaginoscopic hysteroscopy, the modified approach we used in this study, is an atraumatic and acceptable method for the patients,[4,8] we believe that it has an advantage over TVS for the diagnostic approach of endometrial changes caused by tamoxifen. In vaginoscopic hysteroscopy, a speculum is not used and the cervix is not clamped, thereby reducing patient discomfort. General or even local anesthesia is not required. With this method, one also has the ability to visualize the vaginal epithelium.

A recent study suggested that a high-risk group of patients could be identified at the evaluation prior to the initiation of tamoxifen treatment.[9] The fact that in our study patients with abnormal pretreatment findings underwent D&C does not allow us to test this conclusion.

No consensus exists regarding the most appropriate method of surveillance of tamoxifen-treated women. In recent studies, endometrial assessment by TVS is recommended reserving hysteroscopy for women with a thick endometrium.[5,10] Sonohysterography is another method that has been proposed for the evaluation of such patients.[11] Based on the results of our study, we propose sonographic evaluation and vaginoscopic hysteroscopy prior to tamoxifen treatment. In the follow-up visits, these women should undergo TVS, vaginoscopic hysteroscopy, and cytological examination (endometrial brushing-cell block) of the collected sample. Finally, we recommend D&C mostly in symptomatic women with abnormal uterine bleeding.

CONCLUSION

Vaginoscopic hysteroscopy is a modified approach that causes reduced pain and is well tolerated by almost every patient. In addition, the screening of patients with breast cancer receiving tamoxifen can increase significantly the sensitivity and specificity of transvaginal sonography in the detection of endometrial changes. It is recommended in every patient prior to the initiation of treatment and at the follow-up visits.

References:

1. Kedar R, Bourne T, Powles T, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomized breast cancer prevention trial. *Lancet*. 1994;343:1318-1321.

2. van Leeuwen FE, Benraadt J, Coebergh JW et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet*. 1994;343:448-452.

3. Selvaggi L, Bettocchi S, Porreca M, Loverro G. A vaginoscopic approach to hysteroscopy. *J Am Assoc Gynecol Laparosc*. 1995;2:S76.

4. Paschopoulos M, Paraskevaidis E, Stefanidis K, Kofinas G, Lolis D. Vaginoscopic approach to outpatient hysteroscopy. *J Am Assoc Gynecol Laparosc*. 1997;4:13-15.

5. Franchi M, Ghezzi F, Donadello N, Zanaboni F, Beretta P, Bolis P. Endometrial thickness in tamoxifen treated patients: an independent predictor of endometrial disease. *Obstet Gynecol*. 1999;93:1004-1008.

6. Timmerman D, Deprest J, Bourne T, Van den Berghe I, Collins WP, Vergote I. A randomized trial on the use of ultrasonography or office hysteroscopy for endometrial assessment in postmenopausal patients with breast cancer who were treated with tamoxifen. *Am J Obstet Gynecol*. 1998;179(1):62-70.

7. Mourits MJ, Van der Zee AG, Willemse PH, Ten Hoor KA, Hollema H, De Vries EG. Discrepancy between ultrasonography and hysteroscopy and histology of endometrium in postmenopausal breast cancer patients using tamoxifen. *Gynecol Oncol*. 1999;73:21-26.

8. Bettocchi S, Selvaggi L. A vaginoscopic approach to reduce the pain of office hysteroscopy. *J Am Assoc Gynecol Laparosc*. 1997;4:255-258.

9. Berliere M, Charles A, Galant C, Donnez J. Uterine side effects of tamoxifen: a need for systematic pretreatment screening. *Obstet Gynecol*. 1998;91:40-44.

10. Ceci O, Bettocchi S, Marello F et al. Sonographic, hysteroscopic, and histologic evaluation of the endometrium in postmenopausal women with breast cancer receiving tamoxifen. *J Am Assoc Gynecol Laparosc.* 2000;7(1):77-81.

11. Elhelw B, Ghorab MN, Farrag SH. Saline sonohysterography for monitoring asymptomatic postmenopausal breast cancer patients taking tamoxifen. *Int J Gynaecol Obstet.* 1999;67(2):81-86.